
PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES

THIRD EDITION

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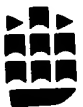
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SECTION B. UPPER RESPIRATORY INFECTIONS

42. THE COMMON COLD

JACK M. GWALTNEY, Jr.

While the designation "the common cold" is a time-honored phrase used by both physician and lay persons alike for the identification of acute minor respiratory illness, current scientific knowledge discloses that there is no basis for the concept of a single entity implied by the use of such a term. Instead, "the common cold" is a group of diseases caused, for the most part, by members of five families of viruses. The viruses in these families have distinctive biochemical properties that govern their differing pathogenic and epidemiologic behavior. In addition, the immunotypes of the different viral families have antigenic variations that are of biologic importance to the immune system of their human host. The problem of controlling acute respiratory disease presents a complex challenge that will require specific approaches suitable for the properties of the individual virus groups. Thus the hope for the development of a single "cure for the common cold" is an unrealistic expectation, which has historically led to the diversion of resources into attempts at simplistic and unrealistic solutions.

As a clinical entity, the common cold is a mild, self-limited, catarrhal syndrome that is the leading cause of acute morbidity and of visits to a physician in the United States. It is also a major cause of industrial and school absenteeism.¹ A small proportion of colds is complicated by bacterial infections of the paranasal sinuses and the middle ear, which require antimicrobial therapy.

Based on early observations of their contagious nature, colds have long been thought to be due to infectious agents. It was not until the isolation of a number of new respiratory viruses in tissue culture in the 1950s that the specific etiology of colds was known. The first of these, a parainfluenza virus, was shown to cause acute respiratory disease in 1955.² In 1956, the first of the rhinoviruses was isolated from adults with common colds.^{3,4} The following year, respiratory syncytial virus was related to acute respiratory illness in infants,⁵ and, in 1958, one of the enteroviruses, coxsackievirus A21, was recovered from military recruits with mild respiratory disease.⁶ The latest group of common cold viruses to be discovered, the coronaviruses, was first reported in the 1960s.^{7,8} Since that time no new cold viruses have been found, although the specific cause of some colds remains unknown. Other respiratory viruses, such as influenza virus and adenovirus, produce the common cold syndrome but are characteristically associated with a more severe illness, which often involves the lower respiratory tract. The discovery of the large number of cold viruses revealed for the first time

the complexity of the problem and indicated that it will be a difficult one to control.

ETIOLOGY

The major respiratory viruses causing colds and similar upper respiratory illnesses are found in the myxovirus, paramyxovirus, adenovirus, picornavirus, and coronavirus groups (Table 1).⁹⁻¹² Within these groups of viruses are many different antigenic types. The rhinovirus group, which accounts for approximately 30 percent of colds in adults, has 100 antigenically different types. The percentage of colds caused by the coronavirus group and the number of serologic types of this virus have not been fully determined, but it is believed that these viruses are an important cause of colds. The three parainfluenza viruses and the respiratory syncytial virus each account for a proportion of colds on an annual basis. Influenza virus and adenovirus produce a spectrum of illness that overlaps the common cold syndrome. Some of the enteroviruses produce coryza, as do some viruses that usually produce more characteristic findings, such as exanthem. Because mild streptococcal pharyngitis cannot be differentiated from viral pharyngitis on clinical grounds, it also is included as a cause of "colds." The etiology of approximately 35 percent of colds in adults remains unknown. Some undiagnosed illnesses may result from the insensitivity of methods currently used for detecting known viruses, and others may be due to undiscovered agents. Colds in children are caused by the same viruses in roughly the same proportion, but the total number of colds that can be diagnosed in children is significantly lower. In some studies, as high as 70 percent of acute respiratory illnesses in children could not be assigned an etiology.

Colds are a frequent illness because of the large number of different causative viruses and also because reinfections may

TABLE 1. Viruses Associated with the Common Cold

	Antigenic Types	Percentage of Cases ^a
Rhinoviruses	100 types and 1 subtype	30-35
Coronavirus	3 or more types	≥10
Parainfluenza virus	4 types	10-15
Respiratory syncytial virus	1 type	
Influenza virus	3 types	
Adenovirus	33 types	
Other viruses (enterovirus, rubella, rubella, varicella)		5
Presumed undiscovered viruses		30-35
Group A β -hemolytic streptococci ^b		5-10

^a Estimated percentage of colds annually.

^b Included because differentiation of streptococcal and viral pharyngitis is not possible by clinical means.

occur with the same virus type. Second infections probably occur with members of all the viral groups; with some, such as coronavirus, reinfections appear to be particularly common. Up to 80 percent of persons infected with coronavirus OC43 have had prior neutralizing antibody to the virus.¹³

SEASONAL INCIDENCE

The respiratory viruses have a worldwide distribution. Annual epidemics of upper respiratory tract disease occur in the colder months in temperate areas and during the rainy season in the tropics. In the United States the respiratory disease season begins in late August to mid-September.^{14,15} Respiratory illness rates rise sharply over a few weeks and then remain elevated until spring. During March, April, and May, rates decline to the low summer level.

The events controlling the seasonal variation in attack rates of acute respiratory disease are not well understood. Adding to the complexity of the problem has been the discovery that some of the virus groups have their own seasonal pattern within the overall respiratory disease season. Rhinovirus outbreaks occur in the early fall and in mid- to late-spring,¹⁵ and coronaviruses are most prominent in the winter.¹³ Studies with a specific virus, rhinovirus type 15, showed that chilling of volunteers did not increase their susceptibility to infection and illness.¹⁶ Thus the effect of thermal cold per se on the host does not appear to be the explanation for the seasonal outbreaks of colds.

Undoubtedly, among the responsible variables for seasonal fluctuations in colds are the bringing together of children during school periods and the increased crowding indoors of populations during colder months.¹⁷ Also, seasonal changes in relative humidity may be an important variable controlling prevalence of the different virus families because of the effect of differing relative humidities on virus survival. In general, enveloped viruses survive better under conditions of low relative humidity, as found in colder months of the year, while the converse is true for nonenveloped viruses.

ATTACK RATES

During peak months in the respiratory disease season in the United States, adults average six to eight colds per 1000 persons per day.¹⁵ In the summer, rates fall to two to three colds per 1000 per day. Overall, adults in the United States average two to four colds per year and children six to eight.^{14,15} In one 10-year study of illness in families, young children in nursery school averaged up to nine colds for the period of September through May! Illness rates decline in older children and reach adult levels in adolescence. Men have slightly more colds than women up to the age of adolescence, but after that the incidence is slightly higher in women, perhaps reflecting their exposure to young children. Adults with children in the home have more colds than those without this exposure.^{14,18} Tonsillectomy does not reduce the incidence of colds.¹⁴ Cigarette smokers have the same incidence of colds as nonsmokers, but the severity of their illness is greater.^{15,19}

TRANSMISSION

The main reservoir of respiratory viruses is in young children. Spread of colds takes place most commonly in the home^{14,18} and school.²⁰ Children acquire new viral strains from their schoolmates, which they then bring home and pass to other family members. Two- to five-day intervals occur between cases. Secondary attack rates of family members vary, depending on age, position in the family, and prior immunity to the virus. Age and immunity are related risk factors. Young children and mothers have high secondary attack rates as a result of close and prolonged exposure to school children in the family. The secondary attack rate of fathers is relatively low.

The mechanism(s) for the spread of cold viruses has not been well established. Possible means of transmission include (1) direct contact with infectious secretions on skin and environmental surfaces, (2) large particles of respiratory secretions that are briefly transported in air, (3) infectious droplet nuclei suspended in air, and (4) combinations of these methods.²¹ For some viruses, such as rhinovirus, close physical contact appears necessary for efficient spread. Infectious rhinovirus is produced primarily in the nose and is shed in highest concentrations in nasal secretions. Peak viral titers in nasal mucus occur on the second to fourth day of experimental infection and coincide with the period of maximum communicability.²¹ A high proportion of persons with natural and experimental rhinovirus colds have recoverable virus on their hands. With experimental rhinovirus infection, brief hand contact permits ready transfer of virus-contaminated nasal secretions from the hands of infected subjects to the hands of susceptible subjects. When the contaminated fingers of the susceptible subjects are then placed in contact with the nasal and conjunctival mucosa, infection results in a high percentage of cases.²² In a recent study, which has not been confirmed, treatment of the fingers with a virucidal solution reduced the rate of infection in mothers exposed to other family members with fresh colds.²³ This latter study provides the only direct evidence on the mechanisms of common cold transmission under natural conditions and suggests that a proportion of colds are spread by a hand contamination/self-inoculation route.

Another rhinovirus transmission model has been developed in which virus is reliably transmitted through the air in large- and/or small-particle aerosol.²⁴ This model demonstrates the feasibility of the aerosol route of spread but does not prove that it occurs under natural conditions. Studies conducted in the field with intervention techniques specific for aerosol transmission are needed to address that question. There is epidemiologic evidence that influenza and adenovirus may spread, at least in part, by small airborne droplets. Thus, all the respiratory viruses may not behave in the same way, and further studies are necessary to determine which route or routes of transmission are important in the natural dissemination of all these viruses.

PATHOGENESIS

Viral invasion of the upper respiratory tract is the basic mechanism in the pathogenesis of colds, but the specific events leading to clinical illness are not well understood. Infection with common cold viruses is characteristically of short duration and self-limited. For example, maximum rhinovirus shedding lasts 3 weeks or less in young adults with experimental colds,^{25,26} and coronavirus excretion has been detected for only 1-4 days.¹³ Cold viruses are not usually present in asymptomatic persons,²⁷ although subclinical infections do occur and viral carriage may be somewhat prolonged in children.²⁸

Characteristic changes have been described in sloughed columnar epithelial cells in nasal secretions of persons with natural colds of unknown etiology.²⁹ Cells with persistent ciliary activity have been found in nasal secretions in the first through the third day of illness. Also, some exfoliated cells show degenerative changes characterized by progressive nuclear pyknosis and the formation of apparent inclusion bodies. More recently ciliated epithelial cells containing viral antigen have been found in the nasal mucus of volunteers with experimental rhinovirus colds.³⁰

Attempts to demonstrate specific histopathologic changes in nasal biopsy specimens of volunteers with rhinovirus colds³¹ or in rhinovirus-infected nasal polyp cultures³² have not been successful. A subsequent study by light and electron microscopy of nasal biopsy specimens from young adults with natural colds confirmed the absence of destruction of the nasal epithelium.³³ In this study there was a significant increase in the number of

uses has not been shown to include (1) direct skin and environmental secretions that droplet nuclei susceptible methods.²¹ For physical contact ap-
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neutrophils in the epithelium and in the lamina propria. The number of epithelial mast cells was not increased. The findings with rhinovirus contrast with the destructive changes to the respiratory epithelium that are seen with influenza virus infection.

With rhinovirus colds, the period of maximum viral excretion in nasal secretions coincides with the peak of clinical illness³⁴ and of appearance of ciliated epithelial cells in nasal mucus.³⁰ At that time, large quantities of protein, including immunoglobulins, are present in nasal secretions. In addition to any direct destructive effect that the virus may have on the respiratory mucous membrane, it is possible that immunologic mechanisms and chemical mediators may play a role in the pathogenesis of the common cold. In this regard, high concentrations of bradykinin and lysylbradykinin have been measured in nasal secretions of volunteers with experimental rhinovirus colds.³⁵ Pathogenic mechanisms for the various respiratory viruses are undoubtedly somewhat different.

The self-limited cold virus infection may lead to pathogenic events that affect the resident bacterial flora of the upper respiratory tract and result in secondary bacterial infection. Bacteria become able to invade normally sterile areas such as the sinuses, middle ear, and perhaps the tracheobronchial tree. The variables involved in triggering invasive bacterial infection are unknown but probably include viral damage to the mucociliary cleansing mechanism of the upper respiratory tract. It is currently unknown whether direct viral invasion of the sinus, middle ear, and tracheobronchial tree is necessary for subsequent bacterial infection to occur or whether the viral involvement can remain localized to the nasal and pharyngeal mucous membrane. However, respiratory viruses have been recovered from sinus³⁶ and middle ear³⁷ aspirates obtained by direct puncture from patients with acute infections at these sites. Abnormalities in eustachian tube function and middle ear pressures have been consistently observed in volunteers with experimental rhinovirus infection.³⁷ During colds, increases have also been noted in titers of resident bacterial populations of the upper airways, but the significance of this is unknown.^{38,39}

CLINICAL CHARACTERISTICS

The incubation period of the common cold varies somewhat with the different viruses but is usually between 48 and 72 hours. The cardinal symptoms are nasal discharge, nasal obstruction, sneezing, sore or "scratchy" throat, and cough.^{14,19} Slight fever may be found, but temperature elevation of more than a degree is distinctly uncommon in the adult. Infants and young children may have more frequent temperature elevation. The early symptoms may be minimal with only mild malaise and nasal complaints. With rhinovirus infection, sneezing, nasal discharge, and nasal obstruction usually begin simultaneously on the first day of illness and rapidly increase to maximum severity by the second or third day. Paralleling the nasal symptoms are sore, dry, or "scratchy" throat. Cough and hoarseness may also begin early in the course of illness and, when present, tend to persist until the end of the first week of symptoms by which time nasal and pharyngeal complaints have usually subsided. Limited information is available suggesting that symptom patterns are similar with coronavirus colds.¹³

The median duration of rhinovirus colds is 1 week, but in approximately one-quarter the illnesses last up to 2 weeks. In cigarette smokers with rhinovirus colds, cough is increased and prolonged. Other complaints include mild burning of the eyes; true conjunctivitis is not seen except in some adenovirus and enterovirus infections. There may also be loss of sense of smell and taste and a feeling of pressure in the ears or sinuses due to obstruction and/or mucosal swelling. The voice may have a nasal quality. Painful maceration of the skin around the nostrils is often bothersome when rhinorrhea has been profuse and persistent.

On physical examination the findings may be few despite the subjective discomfort of the patient. A red nose and a dripping nasal discharge are the characteristic features of the cold sufferer, but many patients have minimal outward manifestations of the infection. The nasal mucous membrane may have a glassy appearance due to the exudation of serum proteins and increased mucus secretions. It is difficult to judge accurately the presence of increased erythema of the mucous membrane of the nose and throat due to normal variations in the color of these structures. Marked pharyngeal erythema and exudate are not seen with rhinovirus and coronavirus infections, but they do occur with pharyngoconjunctival fever of adenovirus infection. Examination of the chest may reveal the presence of rhonchi.

The clinical picture of the common cold is similar in children and adults. However, in young children parainfluenza virus and respiratory syncytial virus infection may lead to viral pneumonia, croup, and bronchiolitis, while in adults these viruses usually cause only colds. In both adults and children the upper airway manifestations of rhinovirus, coronavirus, parainfluenza virus, and respiratory syncytial virus infections are indistinguishable in the individual patient.

DIAGNOSIS

The manifestations of the common cold are so typical that self-diagnosis by the patient is usually correct. Hay fever and vasomotor rhinitis may give similar nasal symptoms, but the recurrent and chronic nature of these diseases is soon recognized by the patient and easily diagnosed by the physician from the patient's history. Diagnosis of the specific virus involved is usually not possible on the basis of clinical observation. Some acute respiratory infections, such as influenza and pharyngoconjunctival fever, when seen in a typical epidemiologic setting, can be recognized without benefit of viral culture or serologic tests. Knowledge of the characteristic seasonal patterns for the different virus groups may also aid in the identification of a particular virus.

The main challenge to the physician is to distinguish the uncomplicated cold from the approximately 0.5 percent of cases with secondary bacterial sinusitis and the 2 percent with otitis media.¹⁴ This is not easy because of the lack of inexpensive and noninvasive diagnostic tests for these infections. A complete examination should be performed on the pharynx, nasal cavity, ears, and sinuses. In the pharynx, marked injection or exudate should raise suspicion of streptococcal or adenovirus infection, Vincent's angina, mononucleosis, or diphtheria. Occasionally, patients have small vesicles on the palate due to coxsackievirus A infections. The presence of nasal polyps is suggestive of an underlying allergic problem. In children, a foreign body may lead to persistent nasal discharge. Examination of the ears is directed at finding changes in the appearance of the tympanum, indicating infection (see Chapter 46). The use of the pneumatic otoscope is helpful in determining if fluid is present behind the ear drum. The sinuses should be examined by transillumination under optimal conditions (see Chapter 47).

Sinus radiography is a sensitive diagnostic test for infection of the sinuses, but the expense of the procedure has prevented its widespread use. The most valuable laboratory test in patients with pharyngeal complaints is rapid antigen detection for group A β -hemolytic streptococci. Many of the respiratory viruses can be isolated in cell culture, although specific virologic diagnosis is not usually available in clinical practice. Rhinoviruses grow in human embryonic lung cells (WI-38), myxo- and paramyxoviruses in primary Rhesus monkey kidney cells, and respiratory syncytial virus in Hep 2 cells. Isolation of coronavirus in cell culture has proved difficult with currently available techniques. The sensitivity of the tests for isolating viruses can vary widely with changes in the sensitivity of the cell cultures.

The serologic diagnosis of influenza, parainfluenza, respiratory syncytial, and adenovirus infection is available in some

state health department laboratories. Serum specimens should be obtained in the acute phase of illness and approximately 3 weeks later and tested simultaneously. A fourfold or greater rise in antibody titer is indicative of infection. Serologic diagnosis of rhinovirus infection is not practical because of the many different antigenic types. Rapid techniques using fluorescent antibody or other immunodiagnostic procedures on respiratory secretions may become practical in the future and would be useful if antiviral chemotherapy becomes available.

TREATMENT

Only symptomatic treatment is available for the uncomplicated common cold. Individual measures directed at controlling nasal and pharyngeal complaints and cough are more effective than all-inclusive cold remedies found in tablets and capsules. Direct application to the nasal membrane of vasoconstrictors such as 0.5 or 0.25% phenylephrine or 1% ephedrine drops or sprays are recommended to provide symptomatic relief of nasal obstructions and to promote drainage of nasal secretions. Patients should be instructed to place themselves in a head down position when administering decongestants to achieve penetration of the drug to inaccessible areas of the nasal cavity. An interval of approximately 1 minute should be allowed between three separate applications of drops or spray. Decongestants should be used every 4 hours on a regular basis. Patients should be cautioned on the rebound effect that results if decongestants are used continuously for more than 3 or 4 days. Recently, it has been shown that intranasal application of a topically active parasympatholytic, ipratropium, was effective in reducing nasal secretions.⁴⁰

Sore throat is relieved by warm saline gargles and cough by liquids or cough drops containing dextromethorphan. Cough suppression in the severe case is best achieved with preparations containing codeine. The regular application of an ointment containing a petrolatum base is useful in controlling painful maceration of the nares. Aspirin and bed rest are of value when headache and constitutional symptoms are prominent. The patient should restrict his activities during the height of the illness, at which time he is most contagious to others. Regular hand-washing and care to avoid contamination of the environment with nasal secretions may also help to prevent spread.

Antibiotics have no place in the treatment of uncomplicated colds, and antihistamines have only a minimal effect in reducing nasal secretions.⁴¹ Until truly effective and specific treatment becomes available, there will continue to be fads in the use of unproven cold remedies. The ingestion of large doses of vitamin C has been widely used as a preventive or therapeutic measure for colds. In some instances, controlled studies have shown a modest beneficial effect of vitamin C for colds. However, a careful analysis of the studies has indicated that a placebo effect could not be ruled out. Many participants correctly surmised from the taste of the contents of the capsules used whether they were receiving vitamin C or a placebo.⁴² In volunteers experimentally infected with rhinovirus, vitamin C in doses of 3 g/day was not effective in preventing infection and illness.^{43,44}

PROSPECTS FOR CONTROL

Vaccine development has reached an impasse because of the discovery of the many different cold viruses, particularly the 100 rhinoviruses. Unless ways are found to combine large numbers of viral antigens effectively or to take advantage of minor antigenic cross-relationships that exist, prospects for common cold vaccines are not good. A number of chemical compounds have inhibitory activity against respiratory viruses in tissue culture systems, and attempts are being made to develop antiviral agents for clinical use. The activity of such compounds tends to be relatively group-specific, but some have shown activity against most of the rhinoviruses.

The most promising approach to control of colds has come through the development of interferon. Topically applied intranasal recombinant human interferon- α_2 has a highly effective prophylactic activity against experimental rhinovirus infection.⁴⁵⁻⁴⁷ When given therapeutically in the same manner, interferon has reduced viral excretion, but its effect on development of illness has been of only minimal to moderate benefit.⁴⁸ In addition, topically applied intranasal interferon, when used longer than approximately 1 week, is associated with local side effects in the nose, such as stuffiness, dryness, discomfort, and pinpoint areas of ulceration.⁴⁹⁻⁵¹ To avoid these problems associated with the biologic properties of interferon, a strategy has been proposed and tested that employs short-term contact prophylaxis by family members exposed to individuals with colds of recent onset. Using this approach, two field studies have observed an approximately 40 percent reduction of total colds and a virtual elimination of rhinovirus-specific infections in exposed individuals.^{52,53} Side effects were avoided by the short duration of application of the interferon. The success of these studies is a cause for optimism, although topical interferon- α_2 apparently failed to prevent colds due to viruses other than those in the rhinovirus group. The failure of a "broad spectrum" antiviral agent, such as interferon, to be effective for all cold viruses emphasizes the reality of the need to develop individual approaches for the different virus groups.

Another approach under investigation is to develop ways to interrupt the transmission of colds. Since spread of some viruses may occur by direct hand contact/self-inoculation, hand-washing and avoiding finger-to-nose and finger-to-eye contact should be practiced, particularly with exposure to a cold sufferer. It may be possible to develop virucidal preparations for use on the hands that interrupt transmission of infection.²³ Also, covering coughs and sneezes with disposable nasal tissues is recommended as a means of controlling aerosol transmission.

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